

## **REMARKS**

### **Status of the Application**

Claims 8 and 10 are under current consideration, and stand rejected.

Applicants respectfully request reconsideration of the application in view of the remarks made herein.

### **Rejection under 35 U.S.C. § 101**

The Examiner has rejected claims 8 and 10 under 35 U.S.C. § 101 because the claimed invention is allegedly not supported by either a specific or substantial asserted utility or a well-established utility. Applicants respectfully traverse the rejection. However, Applicants submit that the rejection has been overcome in light of the arguments below.

Specifically, the Examiner has stated that the asserted utility for the claimed transgenic mice does not appear to be specific and substantial. The Examiner has based the rejection on the evidence of record allegedly not providing a correlation between the phenotypes exhibited by the claimed mice and any disease or disorder. The Examiner further asserts that the evidence of record has failed to provide a correlation between any cerebrus related disease or disorder and the phenotypes exhibited by the claimed mouse. Applicants respectfully disagree. However, although Applicants submit that the correlation has been provided, **and** is well-established in the art, Applicants do not believe that the assertion of such a correlation is necessary for the establishment of utility and for the patentability of the claimed transgenic mouse. For the reasons set forth below, Applicants submit that the Examiner's rejection of the claims for lack of utility is improper.

Claims 8 and 10 and are drawn to a transgenic mouse whose genome comprises a disruption in the nucleotide sequence set forth in SEQ ID NO:1, wherein the mouse exhibits a decrease in average velocity of movement during open field testing, a decrease in total distance traveled during open field testing, an increase in the number of fecal boli during open field testing, or a decrease in total time immobile during the tail suspension test, and to a method of making said transgenic mouse. Applicants have asserted in the specification several potential uses for the transgenic knockout mouse, and such uses of transgenic knockout mice are well accepted within the art. See, for example, page 3, lines 18-26, page 4, lines 12-21 and page 18, line 15 through page 20, line 5, of the specification. The potential uses specifically relate to using the mice to discover, examine and/or develop treatments, including therapeutic agents, capable of modulating

the phenotypes exhibited by the mice, and in particular, capable of modulating the anxiety related behavior and anti-depressant behavior exhibited by the mice. Although Applicants have suggested these potential uses for the transgenic mice, many well-established uses for the mice would be recognized by a person skilled in the art.

Applicants submit that in order to satisfy the utility requirements set forth in 35 U.S.C. § 101, the specification must assert a specific and substantial utility that is credible to a skilled artisan, or the utility of the claimed invention must be apparent to the skilled artisan. See MPEP § 2107. Applicants submit that the instant specification satisfies these requirements.

The instant specification has demonstrated that disruption of the sequence set forth in SEQ ID NO:1 in a mouse results in a phenotype specific to that mouse. In particular, the transgenic mice whose genomes comprise this disruption exhibit several anxiety related phenotypes in the open field test (decreased average velocity, decreased total distance traveled and increased number of fecal boli) and a decreased susceptibility to depression in the tail suspension test (See page 51, lines 7-27 of the specification, Tables 1 and 2, and Figures 3 and 4). The phenotypic parameters of the transgenic mice were evaluated in controlled studies, which are well-established as tests for anxiety and depression.

It is generally accepted in the art that transgenic knockout mice, such as those described in and claimed by the instant application, represent a valuable tool for determining the function of genes in various conditions or disorders. It is also generally accepted that gene function is related to and representative of that of human, in light of the homology between the mouse and human genomes. This is why knockout mice represent such a valuable tool. In the present case, the transgenic mouse described in the instant specification would be accepted by the skilled artisan as a model for the role of the cerebrus gene represented by SEQ ID NO:1. Applicants' disclosure related to the phenotypes of the transgenic mice has established that this gene plays a role in the conditions or disorders of anxiety and depression, as noted above. The value of such an *in vivo* model of cerebrus gene function would be immediately recognized by a person skilled in the art. This is supported by the trend to produce such transgenic mice with disruptions in virtually every gene.

The Examiner has stated that no correlation has been established between the anxiety and depression phenotypes and any disease or disorder. As noted above, Applicants do not believe that this is a requirement to establish that the transgenic mice have utility. However, despite

Applicants' belief that no such requirement exists, Applicants submit that the correlation between the phenotypes exhibited by the transgenic mice and the conditions or disorders of anxiety and depression are recognized within the art and are provided by Applicants' disclosure (see page 24, lines 12-23 and page 21, lines 13-23, respectively).

The Examiner has cited Crabbe (*Science*, 1999, Vol. 284, pp 1670-1672) as establishing that results obtained from behavioral studies, and in particular the open field test, are greatly influenced by the genetic background of the tested mouse. However, the Crabbe reference fails to establish that phenotypic differences between a transgenic knockout mouse and a wild-type control mouse, such as those described in the instant specification, are not real and a result of the disruption of the target gene. In particular, the Crabbe reference compares only one null mutant strain (for the 5-HT1B gene) to inbred wild-type strains, and is not representative of a comparison of all mutant knockout mice and their wild-type control counterparts. Further, the number of mice tested was low, and, even according to the reference, "made formal statistical assessment of reliability infeasible" (see page 1671, column 3, first full paragraph). The Crabbe reference also states that the results obtained in their study can be interpreted in different ways. The open field test is well-recognized by the skilled artisan as a model for the disorder of anxiety, and a connection between the anxiety related phenotypes exhibited by the claimed mouse and the disorder of anxiety would be clear to the skilled artisan. Applicants submit that the Crabbe reference fails to establish that this correlation does not exist.

With regard to the tail suspension test, the Examiner has cited Liu (*Biol Psychiatry*, 2001, Vol. 49, pp 575-581) for establishing differences in this test with respect to gender and genetic background. However, the Liu reference relates to the differences in imipramine response in the tail suspension test between strains, and does not relate to a comparison of the effect of genetic disruption in the tail suspension test, especially within a well-controlled study comparing the knockout mouse to a wild-type control mouse, as was used to test the mice in the instant invention. Liu describes the tail suspension test as "a well-validated test to screen for antidepressants in mice..." and states that the test "has been extensively validated as a screen for antidepressant activity with an impressive diversity of antidepressants... and even electroconvulsive therapy" (see page 575, column 2). The Liu reference does not dispute that immobility time in the tail suspension test is related to the disorder of depression, as the Examiner has suggested. The Liu reference supports the tail suspension test as a well-accepted model for depressive behavior. The

Examiner has cited the Liu reference for showing gender and strain differences in the tail suspension test. Liu does not address what relative differences would be observed between transgenic knockout and wild-type (non-transgenic) control mice among these strains. The tail suspension test in the instant invention addresses this issue by comparing the cerebrus knockout mice to age-, gender- and strain-matched control mice. Therefore, the Liu reference fails to support the Examiner's suggestion that no correlation has been established between immobility time in the tail suspension test and the disorder of depression.

Applicants submit that they have demonstrated in the arguments above and in the originally filed specification that a correlation between the phenotypes exhibited by the claimed mice and the disorders of anxiety and depression are well-established. However, even in the absence of this correlation, the transgenic mice have been demonstrated as useful for discovering treatments, including therapeutic agents, capable of modulating a phenotype exhibited by the mice. As noted above, Applicants are not aware of any requirement for a correlation between a phenotype and a specific disease in order to establish the utility of a transgenic mouse. Applicants submit that the utility of a transgenic knockout mouse such as that claimed herein would be immediately apparent to the skilled artisan.

In summary, Applicants have asserted in the specification several specific and substantial uses for the claimed transgenic mice. Further, in light of the art-recognized value of and demand for transgenic knockout mice, the asserted utilities are among many that are well-established and credible to the skilled artisan.

In view the arguments set forth above, Applicants believe the rejection of the claims under 35 U.S.C. § 101 is improper, and respectfully request withdrawal of the rejection.

**Rejection under 35 U.S.C. § 112, first paragraph**

The Examiner has rejected claims 8 and 10 under 35 U.S.C. § 112, first paragraph, because one skilled in the art would allegedly not know how to use the claimed invention as a result of the alleged lack of either a specific or substantial asserted utility or a well-established utility for the reasons set forth in the utility rejection. Applicants respectfully traverse the rejection. However, for the reasons set forth above in response to the utility rejection, Applicants submit that the rejection under 35 U.S.C. § 112, first paragraph, is improper. Therefore, Applicants respectfully request withdrawal of the rejection.

It is believed that the claims are currently in condition for allowance, and notice to that effect is respectfully requested. The Commissioner is hereby authorized to charge any deficiency or credit any overpayment to Deposit Account No. 50-1271 under Order No. R-67.

Respectfully submitted,

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